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CYCLOPENTA-FUSED ISOMERS OF BENZ(A)ANTHRACENE

IDENTIFICATION OF MAJOR MICROSOMAL METABOLITES

by

R. Sangaiah[1], A. Gold[1], G. E. R. Easterling[2], R. Watts[2], B. J. Bryant[3], S. Ellis[3], K. Rudo[3], and S. Nesnow[2]

[1]Department of Environmental Sciences and Engineering, University of North Carolina at Chapel Hill, Chapel Hill, NC 27514
[2]Carcinogenesis and Metabolism Branch, Health Effects Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711
[3]Northrop Services, Inc., Research Triangle Park, NC 27709

HEALTH EFFECTS RESEARCH LABORATORY
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
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[2]Health Effects Research Laboratory, U.S. EPA, Research Triangle Park, NC 27711
[3]Northrup Services, Inc., Research Triangle Park, NC 27709

16. ABSTRACT

The microsomal metabolism of a variety of polycyclic systems has been investigated as part of an interest in structure-activity relationships governing cytochrome P-450 mediated bioactivation of polycyclic aromatic hydrocarbons (PAH). Considerable effort has recently been devoted to non-alternate PAH containing a fused five-membered ring, since many compounds in this class, such as cyclopenta(cd)pyrene and the benzofluoranthenes, are both mutagenic and carcinogenic. We report on the metabolism of a series of four cyclopenta-PAH isomers formed from benz(a)anthracene by fusing a five-membered ring between C4-C5 [benz(k)acephenanthrylene, B(k)A], C6-C7 [benz(e)aceanthrylene, B(e)A], C7-C8 (benz(j)aceanthrylene, B(j)A], and C11-C12 [benz(l)aceanthrylene, B(l)A]. The metabolite profiles of these PAHs have been determined with Aroclor-1254, 5,6-benzoflavone and phenobarbital induced rat liver microsomes and the major metabolites unequivocally identified. In accord with the expected reactivity of the cyclopenta double bond towards epoxidation, the corresponding dihydrodiols are major metabolites of each of the PAHs. For B(l)A, and B(j)A, metabolites at the K-region are also observed. For for B(e)A, formation of the 9,10-dihydrodiol (distal to the pseudo bay formed by the cyclopenta ring) is another major pathway. The mutagenicity of these PAHs is described in the following abstract.

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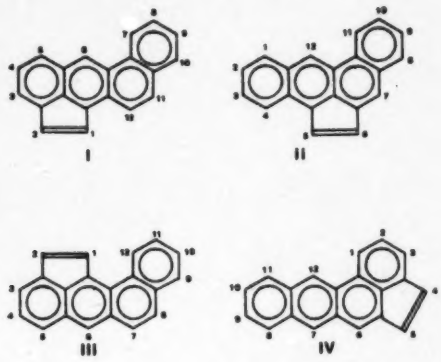
CYCLOPENTA-FUSED ISOMERS OF BENZ(A)ANTHRACENE. IDENTIFICATION OF MAJOR MICROSOMAL METABOLITES.

R. SANGAIAH[1], A. GOLD[1], G. E. R. EASTERLING[2], R. WATTS[2], B. J. BRYANT[3], S. ELLIS[3], K. RUDO[3] and S. NESNOW[2]. [1]Department of Environmental Sciences and Engineering, University of North Carolina at Chapel Hill, Chapel Hill, NC 27514; [2]Carcinogenesis and Metabolism Branch, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711; [3]Northrop Services, Inc., Research Triangle Park, NC 27709.

INTRODUCTION

Efforts to broaden understanding of bioactivation of PAH have recently generated considerable interest in the P450 mediated metabolism and biological activity of nonalternant PAH systems with and without bay regions. Thus, the mutagenic and carcinogenic activity of cyclopenta-(cd)pyrene[1-5], 1,2,3-indeno(cd)pyrene[6] and the benzo fluoranthene isomers[7-9] has been demonstrated and investigations into the metabolism of these compounds initiated. In an extension of research into mutagenicity and metabolism of nonalternant systems, cyclopenta-fused isomers I-IV of benz(a)anthracene have been synthesized[10,11] and shown to be active mutagens in both bacterial and mammalian cells. Towards continued progress in establishing mechanisms of biotransformation of I-IV (Figure 1) and in identifying metabolite features associated with biological activity, characterization of metabolites of this series of PAH will be presented in this report. Of particular interest for I-III is the extent to which biological activity might correlate with epoxidation of the 5-membered ring. The epoxides can open to benzylic carbonium ions which have larger delocalization energies (ΔEdeloc/β) than the highly active C_{10} carbonium generated from the 7,8-diol-9,10-oxide of benzo(a)pyrene or any other possible diolepoxide-derived carbonium ion of I-IV (Table I). Hence, if electronic considerations are a dominant influence, epoxidation of the cyclopenta-fused rings of I-III should lead to

FIGURE 1. STRUCTURES AND NUMBERING CONVENTION FOR COMPOUNDS I-IV



high levels of biological activity by the criterion of $\Delta E_{del}/\beta$ established for Bay Region diolepoxides[12]. The 5-membered ring epoxide of IV does not yield a highly stabilized carbonium ion (Table I) and may therefore not be crucial to biological activity.

MATERIALS AND METHODS

PAH. Compounds I-IV were synthesized and purified by published methods[10-11] and were shown to be pure by HPLC prior to use in metabolism experiments (refer to Figure 1 for nomenclature and numbering convention). The 1,2-oxide of III and the corresponding dihydrodiols were also synthesized and purified by published procedures.[13,14]

Metabolite characterization. Separated metabolites were characterized by UV-vis spectroscopy in methanol on a Coleman 124 spectrohotometer EI mass spectra, both high resolution for elemental composition of the molecular ion and low resolution for fragmentation pattern, were obtained on a VG7070F mass spectrcmeter equipped with a VG 2035F/B data processing system. High field ^{1}H NMR spectra were recorded on a Bruker WM250 spectrometer. Accurate mass determinations

and fragmentation patterns were consistent with all dihydrodiol (dhdo) structural assignments and with the single phenol metabolite identified (Table II). Separation of metabolites was accomplished with a DuPont 850 HPLC by gradient

TABLE I

Delocation energies (ΔEdeloc/β) of the most stable benzylic carbonium ions derived from epoxides from PAH

Epoxide	Carbonium ion	ΔEdeloc/β
I,1,1-oxide	C1	0.879
II,5,6-oxide	C5	0.879
III,1,2-oxide	C1	0.833
IV,4,5-oxide	C5	0.722
BP,7,8 diol-9,10-oxide	C10	0.794

elution chromatography with a methanol-water mixture on a 6.4 mm x 25 cm Zorbax ODS column. The gradient program was as follows for II and III: initial segment 80 → 70% MeOH in 10 min, concave profile (exponent-3 on Dupont programmer); 70 → 100% MeOH in 3 min, convex profile (exponent -9, Dupont programmer); 100% methanol for 10 min. The program for I and IV was: 70-100% methanol in 10 min, concave profile (exponent +3, Dupont programmer; 100% MeOH for 10 min. Chromatographic traces were obtained with a UV detector at 254 nm. Rigorous quantitation of metabolites cannot be accomplished by the analytical methods employed in this study. However, metabolite yields from the chloroform extracts of metabolism mixtures could be approximately ordered by comparison of the signal-to-noise ratios of the ^1H NMR spectra of samples accumulated from an equal number of semi-preparative HPLC runs, made up to equal volumes in acetone-d_6 and generated from the same number of transients (4×10^4). It must be borne in mind that conjugates were not determined; therefore relative yields established in this work

could be altered by future studies with labeled PAH in which total metabolite disposition was determined. In the presentation of the ^1H NMR traces, resonances from impurities are denoted by x and form solvent by s.

RESULTS

Features common to electronic and ^1H NMR spectra of certain metabolites were useful in assigning structures. Saturation of the cyclopenta double bond leaves the benz(a)-anthracene chromophore having the characteristic electronic spectrum shown in Figure 2. Hence,

FIGURE 2. UV-vis of benz(a)anthracene (MeOH).

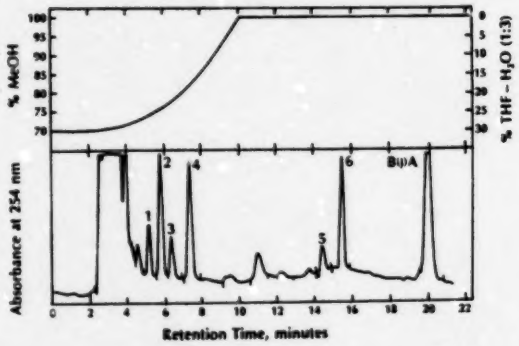
appearance of the benzanthracene-like electronic spectrum indicates metabolism to the cyclopenta-ring dihydrodiol. Partial saturation of the terminal benzo ring by dihydrodiol formation generates a chromophore similar to acephen-anthrylene, while partial saturation of the angular benzo ring produces an anthracene-like

chromophore, aiding in identification of terminal and angular ring dihydrodiols.

The protons of the highly olefinic cyclopenta-bond have a characteristic AX signal[10,11] in the ^{1}H NMR, with $J_{AX} \sim 5$ Hz. The presence of this AX quartet in a metabolite ^{1}H NMR is conclusive evidence that the cyclopenta ring has not been altered. Protons adjacent to 3-sided aromatic bays of I, II, IV or the 4-sided "psuedo fjord"[15] of III are highly deshielded by ring current[16] and appear at low field, well separated from other aromatic signals. The identification of such highly deshielded protons in metabolite NMR spectra therefore indicates that the rings forming bays or fjords retain aromaticity and rules out metabolite structures in which the aromaticity of bay or fjord peripheries is interrupted.

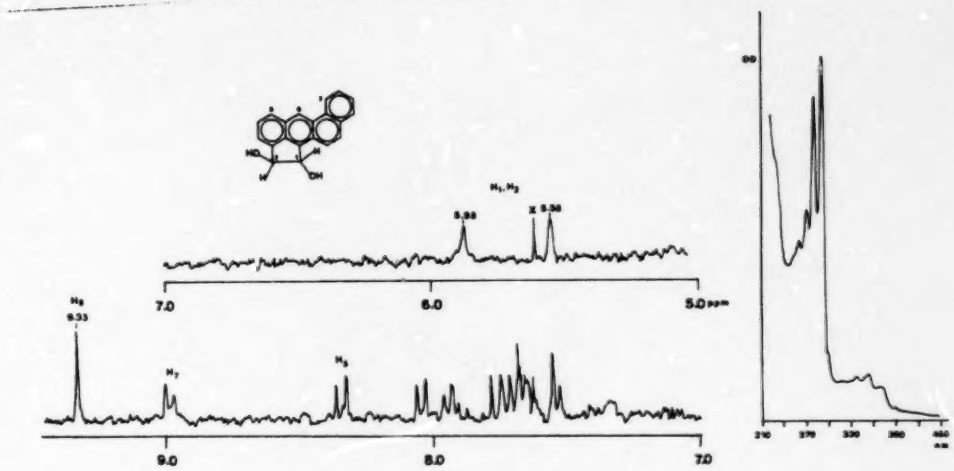
B(j)A(I). Metabolites I_1, I_2, I_4 and I_6 (Figure 3) have been assigned structures; relative

FIGURE 3. HPLC trace (254) and gradient program of metabolite mixture from benz(j)aceanthrylene Peak 1, 11,12-dhdo(I_1); 2, 1,2-dhdo(I_2); 4, 9,10-dhdo(I_4) and 6, 10-OH (I_6)



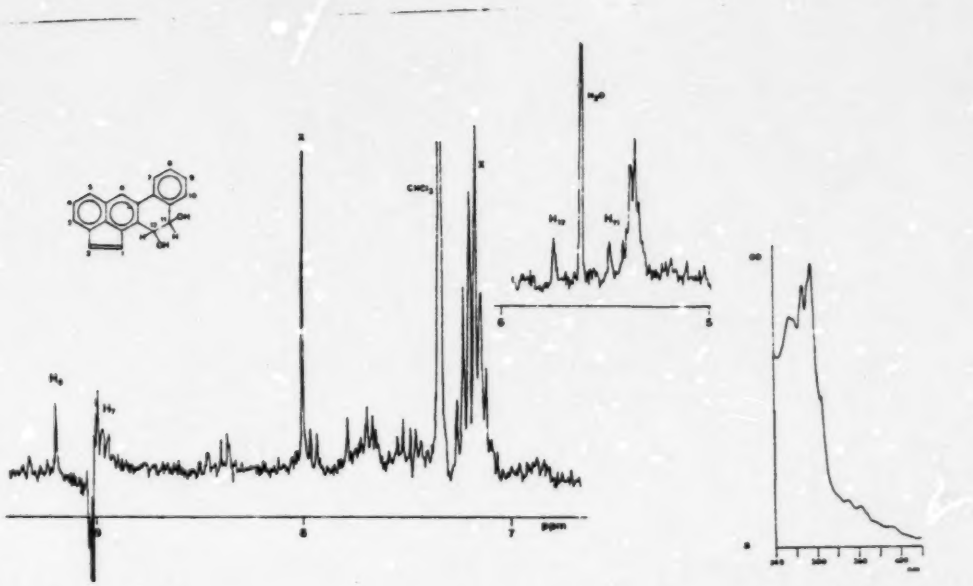
yields are estimated to be $I_2 > I_4 > I_6 > I_1$. The principal metabolite I_2 (Figure 4) has been identified as the 1,2-dihydrodiol arising from

FIGURE 4. Metabolite I_2, ^1H NMR (250 MHz, acetone-d_6, 29°) and UV-vis (MeOH).



epoxidation of the 5-membered ring. Its electronic spectrum resembles that of benzanthracene. In the ^1H NMR, resonances characteristic of bay region protons are present, while absence of vinylic resonances rules out partial saturation of the terminal or angular benzo rings and absence of the cyclopenta AX quartet precludes a k-region dihydrodiol formulation. Metabolite I_1 (Figure 5) was assigned the k-region dihydrodiol structure and was distinguished from I_2 chiefly on the basis of its electronic spectrum, which does not arise from the benzanthracene chromophore. Proton resonances from solvent and HPLC column impurities, which appear as major signals because of the low concentration of I_1, obscure the region where AX quartet should be observed. However other features of the ^1H NMR spectrum was consistent with the structural assignment: a low field singlet and doublet, indicating an aromatic bay region periphery and absence of vinylic resonances

FIGURE 5. Metabolite I_1. ^1H NMR (250 MHz, acetone-d_6, 29°) and UV-vis (MeOH)



precluding terminal or angular benzo ring metabolism. Characterization of I_4 as the 9,10-dihydrodiol (Figure 6) rests partly upon the similarity of its electronic spectrum to that of anthracene, consistent with disruption of angular benzo ring aromaticity. A crucial feature of the ^1H NMR spectrum is the presence two vinyl resonances, since a possible dihydrodiol on the bay region side of the terminal ring would have only a single vinylic signal. The marked downfield position of one of the vinyl signals is consistent with location of a vinyl proton in the bay region, deshielded by the ring current of the adjacent residual anthracene nucleus. I_6 was recognized as a phenol (Figure 7) by relative retention time in the HPLC, molecular weight, elemental composition and the long wavelength band in the electronic spectrum indicating preservation of the benz(j)-aceanthrylene nucleus. Positional isomerism was established by analysis of the first-order

FIGURE 6. Metabolite I_1. ^1H NMR (250 MHz, acetone-d_6, 29°) and UV-vis (MeOH)

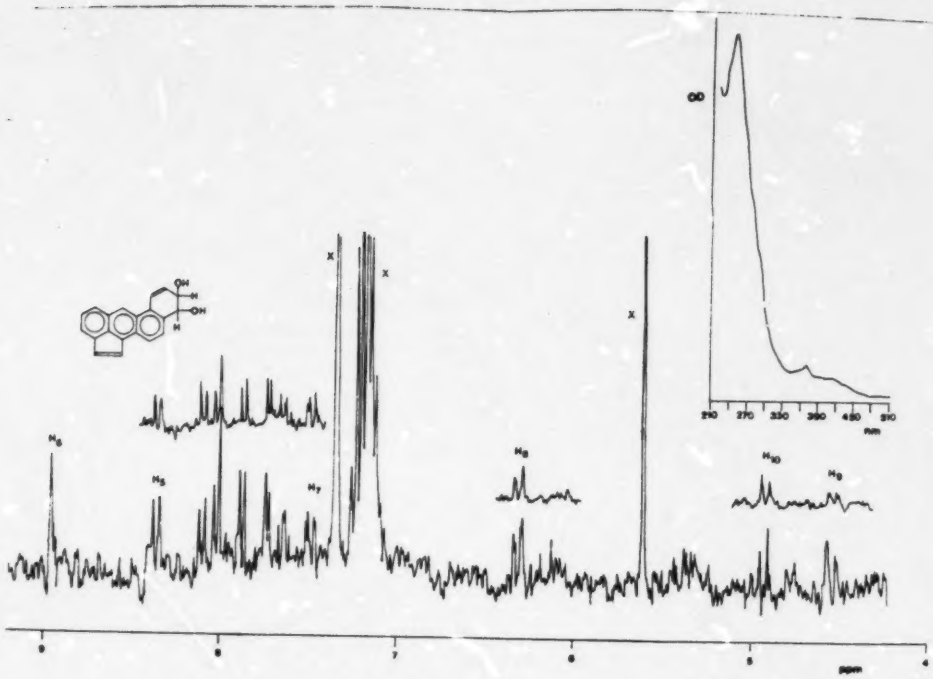
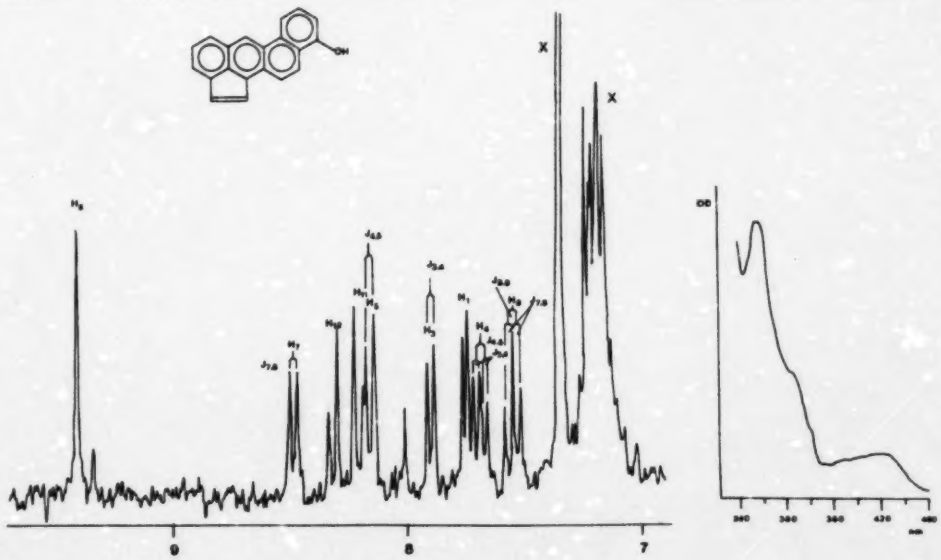


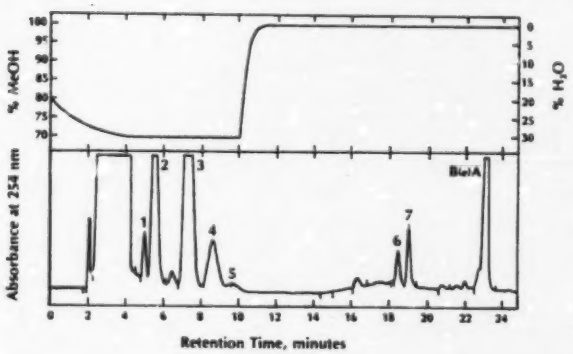
FIGURE 7. Metabolite I_6. ^1H NMR (250 MHz, acetone-d_6, 29°) and UV-vis (MeOH)



couplings of the ^1H NMR spectrum. Absence of a downfield AB or AX quartet rules out substitution of the terminal ring. The presence of two highly deshielded bay region signals is inconsistent with a C_6 or C_7 phenol, while substitution of the k-region would have resulted in the presence of a second aromatic singlet. Upfield shift of a single aromatic proton from the "ortho effect" of hydroxy substitution[17], rules out substitution of C_9 leaving, the 10-OH derivative as the only possibility.

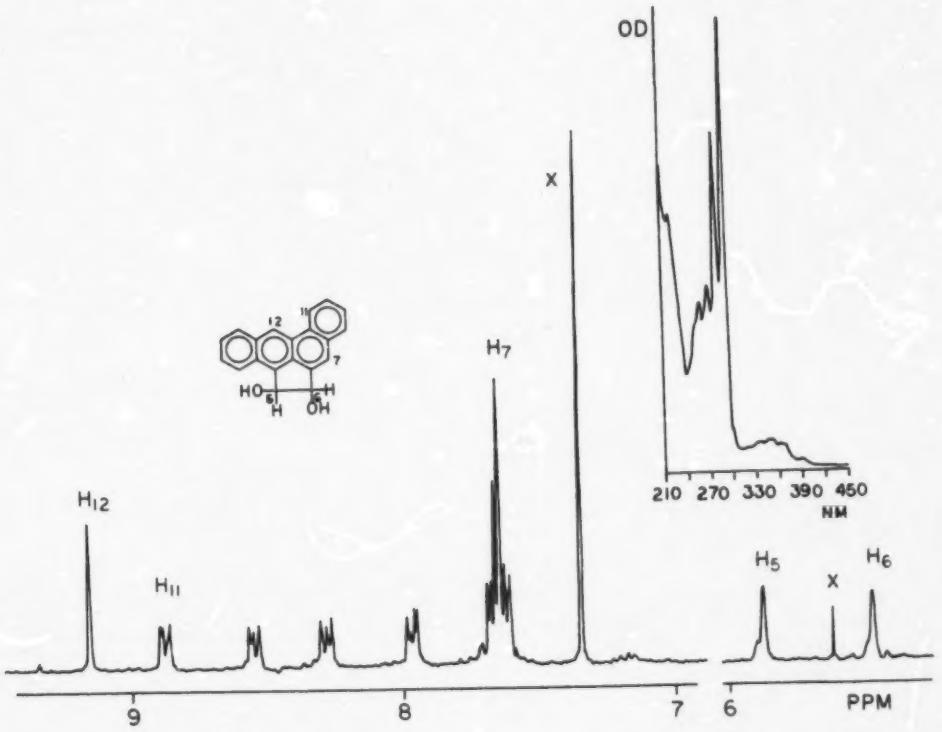
B(e)A(II). Metabolites II_2, II_3, and II_5 (Figure 8) could be assigned structures. Relative

FIGURE 8. HPLC trace and (254 nm) and gradient program of metabolite mixture from benz(e)aceanthrylene. Peak 2, 5,6-dhdo (II_2); 3, 3,4-dhdo (II_3); 5, 1,2-dhdo (II_5)



abundances are estimated $II_2 \sim II_3 > II_5$. II_2 was identified as the 5,6-dihydrodiol (Figure 9) by its benzanthracene-like electronic spectrum and by the absence of vinylic resonances and a cyclopenta AX quartet in the ^1H NMR. II_3 and II_5 were identified as the terminal ring dihydrodiols by the similarity of their similarity of their electronic spectra to that of acephenanthrylene[18,19] and the presence of aromatic bay region signals in the ^1H NMR. The meso bay region

FIGURE 9. Metabolite II_2. ^1H NMR (250 mHz, acetone-d_6, 29°) and UV-vis (MeOH)



proton resonance (H^{12}) of the isomer with the dihydrodiol distal to the bay region is expected to be shifted upfield relative to the resonance of the bay region proton (H12) on the angular ring.[20] On this basis, II_3 is the 3,4-dihydrodiol (Figure 10) and II_5 , the 1,2-isomer (Figure 11).

FIGURE 10. Metabolite II_3. ^1H NMR (250 MHz, acetone-d_6, 29°) and UV-vis (MeOH)

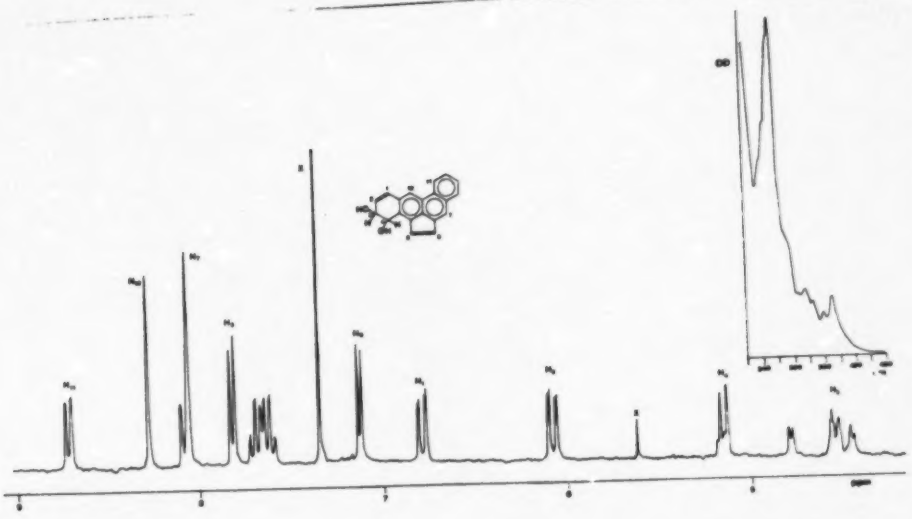
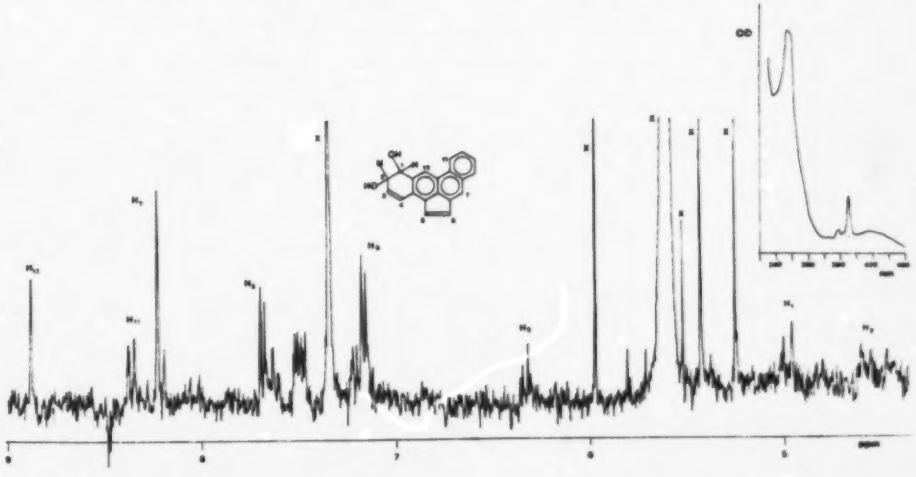


FIGURE 11. Metabolite II_5. ^1H NMR (250 MHz, acetone-d_6, 29°) and UV-vis (MeOH)



B(l)A(III). Metabolites III_3, III_5 and III_6 (Figure 12) were identified. The relative amounts were $III_6 > III_3 >> III_5$. III_3 was identified as the 1,2-dihydrodiol (Figure 13) by its benzanthracene-

FIGURE 12. HPLC trace (254 nm) and gradient program of metabolite mixture from benz(l)-aceanthrylene. Peak 3, 1,2-dhdo (III_3); peak 5, 4,5-dhdo (III_5); peak 6, 7,8-dhdo (III_6)

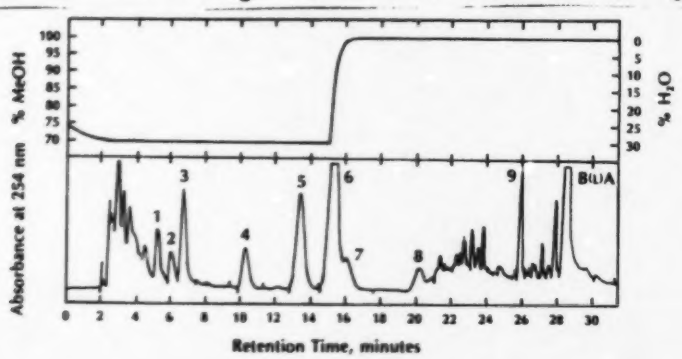
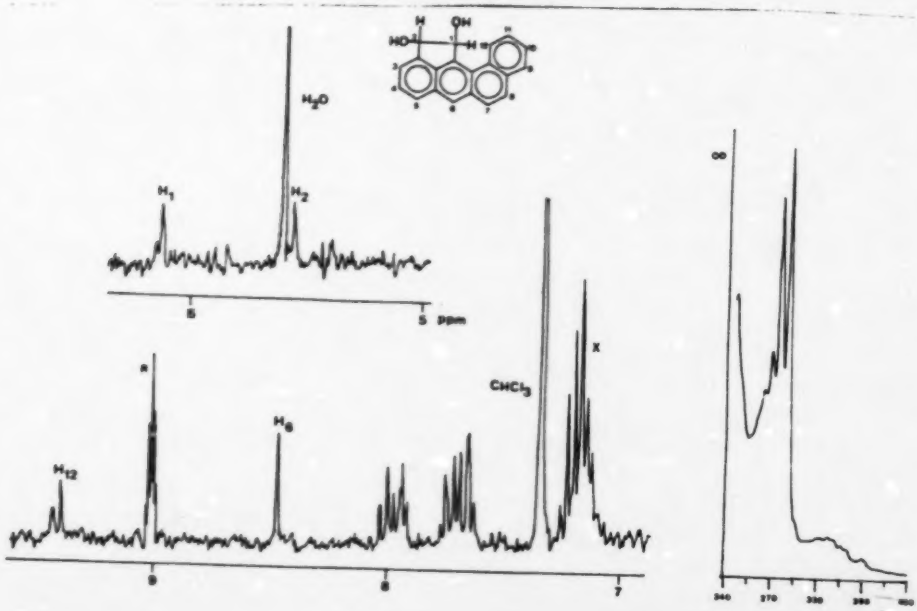
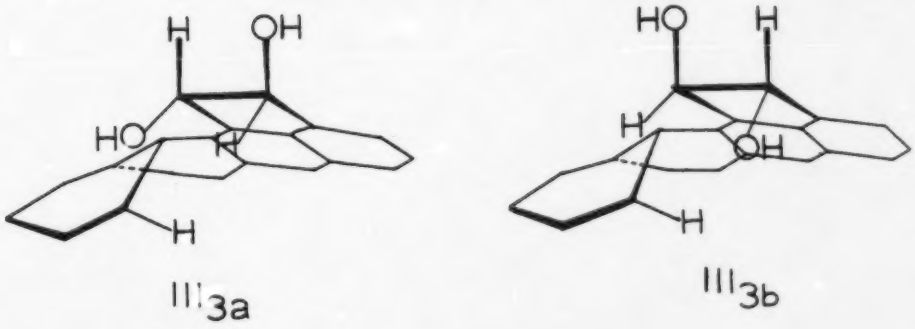


FIGURE 13. Metabolite III_5. ^1H NMR (250 MHz, acetone-d_6, 29°) and UV-vis (MeOH). Resonance R is a reflection of the peak from solvent residual protons



like electronic spectrum and by the absence both of vinylic proton resonances and of a cyclopenta AX quartet in the ^{1}H NMR. Severe steric crowding within the "psuedo fjord" requires III_3 to adopt a non-planar configuration, presumably analogous to the helical configuration adopted by benzo(c)phenanthrene[21]. As a result, two isomeric trans dihydrodiols are possible (Figure 14). Both

FIGURE 14. Configurations of the two possible trans dihydrodiols resulting from the helical configuration III_3



III_{3a} III_{3b}

dihydrodiols have been synthesized, resolved by HPLC and characterized (Figure 15). Under the reasonable assumption that m-chloroperoxybenzoic acid oxidation of III yields an epoxide oriented away from the pseudo fjord, the structural assignments III_{3a} and III_{3b} have been derived for the synthetic dihydrodiols. The metabolite corresponds by HPLC retention time and ^{1}H NMR (Figure 16) to the isomer in which the hydroxyl at C1 is oriented away from the pseudo fjord (III_{3b}).

FIGURE 15. Synthetic routes to the trans dihydrodiol isomers III_{3a} and III_{3b}

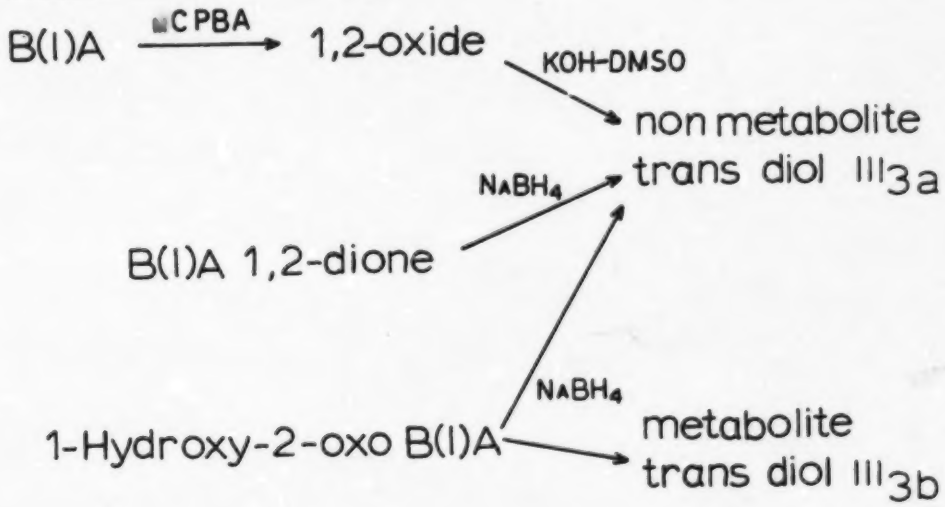
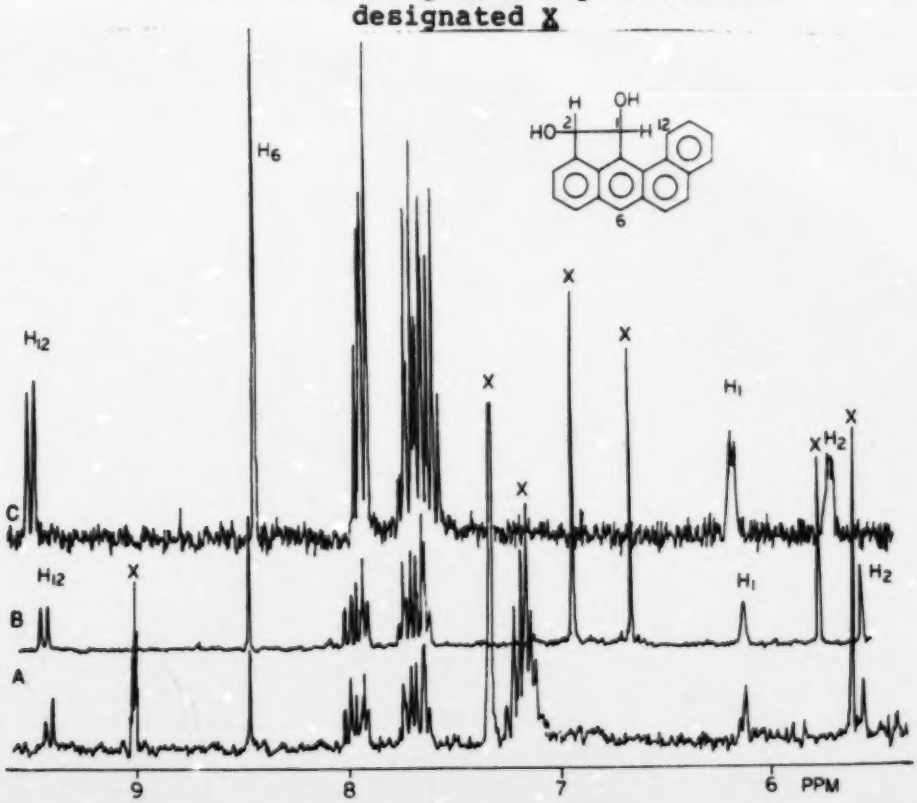


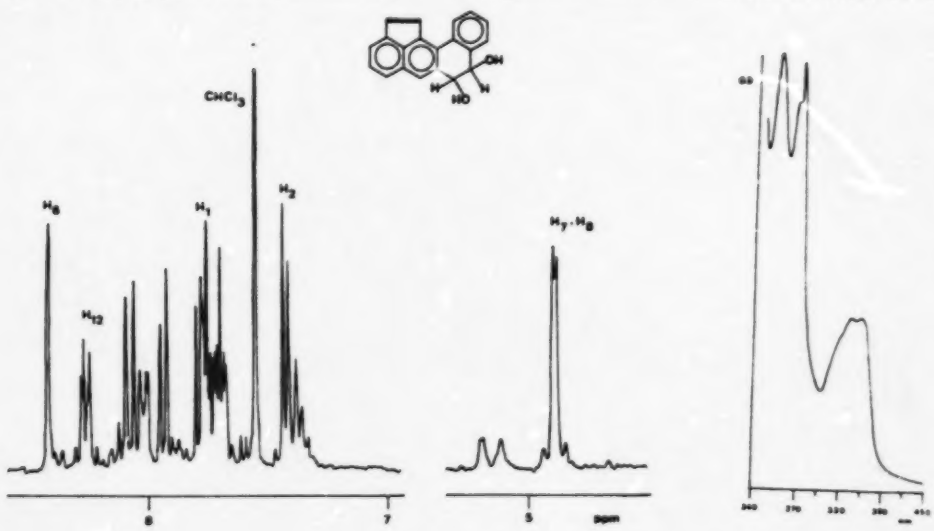
FIGURE 16. ^1H NMR (250 MHz, acetone-d_6, 29°) (a) Metabolite III_3; (b) trans dihydrodiol $III_{3a,b}$ Resonances arising from impurities are designated X



Metabolite III_6 is the k-region dihydrodiol (Figure 17). The electronic spectrum does not indicate a benzanthracene chromophore and the ^1H NMR, while having no vinylic signals, does exhibit the AX quartet of the unsaturated cyclopenta ring. The carbinyl protons appear as a true AB the quartet, typical of the similar magnetic environments of k-region[16] positions.

The electronic spectrum of III_5 (Figure 18) suggests that the terminal benzo ring has been partially saturated, leaving a phenanthrene

FIGURE 17. Metabolite III_6. ^1H NMR (250 MHz, acetone-d_6, 29°) and UV-vis (MeOH)



aromatic nucleus. The most likely formulation for a terminal ring dihydrodiol is the 4,5-diol, and this structure is confirmed by the ^1H NMR. The critical feature is the presence of only a single vinyl resonance allylically coupled to a carbinyl proton.

B(k)A. Two metabolites, IV_1 and IV_2, were collected in sufficient quantity for characterization (Figure 19). IV_1 was the predominant metabolite. The electronic spectrum of IV_1

FIGURE 18. Metabolite III_5. ^1H NMR (250 MHz, acetone-d_6, 29°) and UV-vis (MeOH)

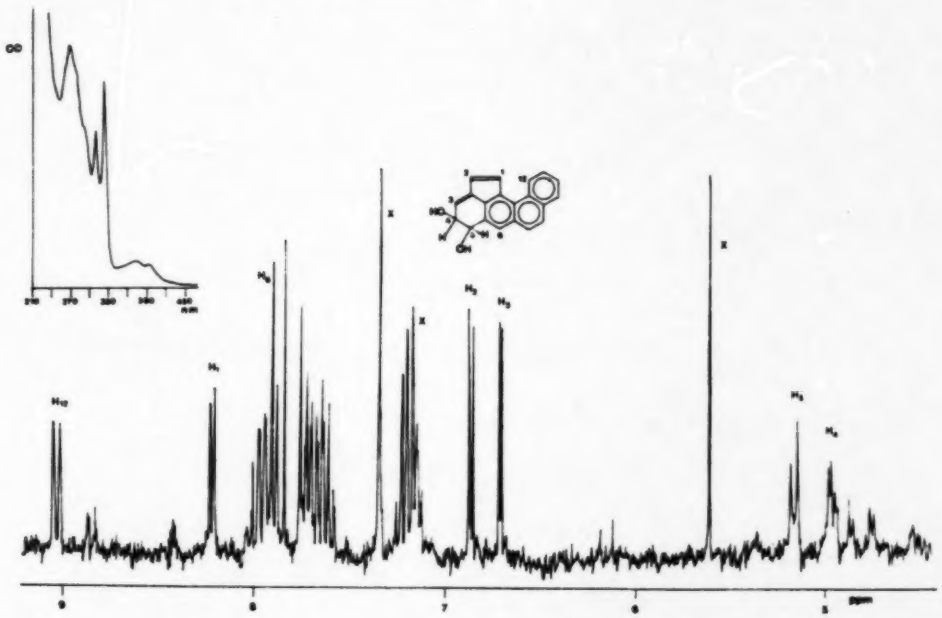


FIGURE 19. HPLC traces (254 nm) and gradient program of metabolite mixture from benz(k)-acephenanthrylene. Peak 1, 4,5-dhdo (IV_1; Peak 2, 8,9-dhdo (IV_2)

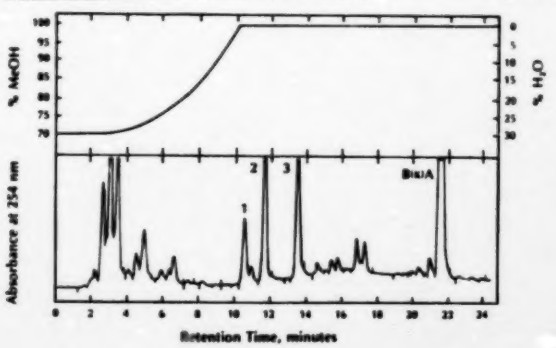
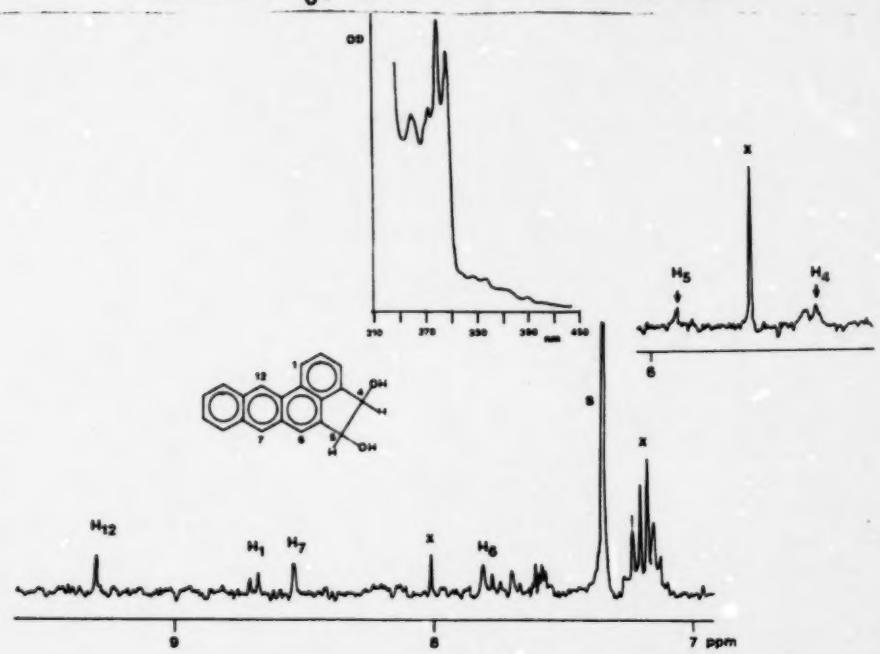


Figure 20), while differing somewhat from that of benzanthracene, was identical to that of 4,5-dihydro IV; hence, IV_1 is the cyclopenta dihydrodiol. The ^1H NMR substantiates this assignment: vinyl resonances and a cyclopenta AX quartet are

FIGURE 20. Metabolite IV_1. ^1H NMR (250 MHz, acetone-d_6, 29°) and UV-vis (MeOH)



absent, with carbinyl protons accounting for only nonaromatic signals in the spectrum. The electronic spectrum of IV_2 (Figure 21) suggests partial saturation of the terminal benzo ring. The 8,9-dihydrodiol (distal to the bay region) is assigned on the basis of the chemical shift of the meso bay region proton according to the same rationale[20] applied to metabolites II_3 and II_5.

The sharp, low concentration maximum in S-9 dependence of mutagenicity of I-III in TA 98 (Figure 22) suggests activation by one-step epoxidation of the cyclopenta bond. Epoxide hydrolase rather than being required for formation of a proximate mutagen dihydrodiol intermediate as in

FIGURE 21. Metabolite IV_2. ^1H NMR (250 MHz, acetone-d_6. 20°) and UV-vis (MeOH)

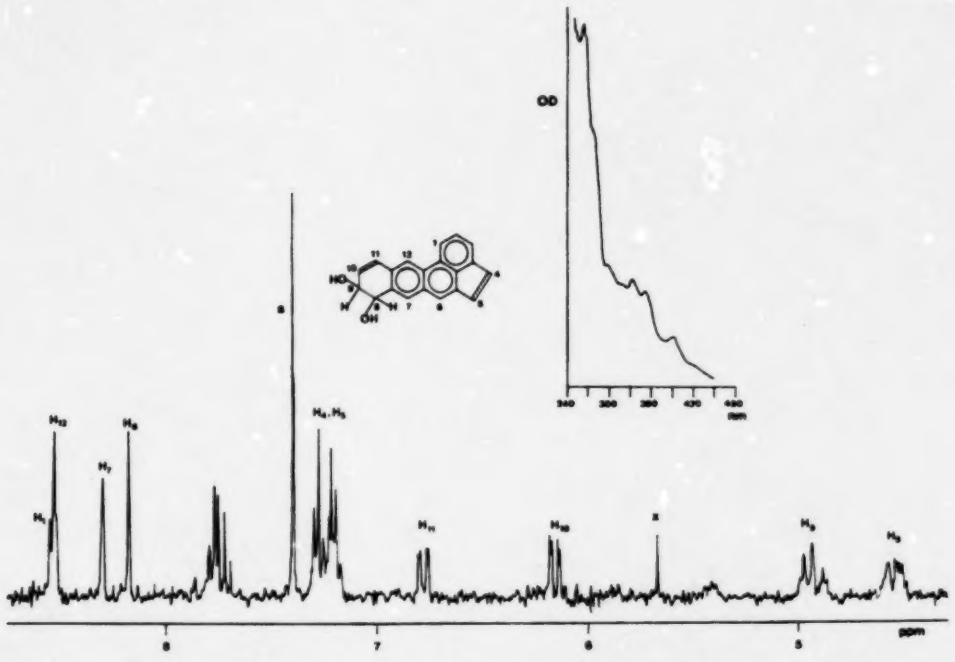
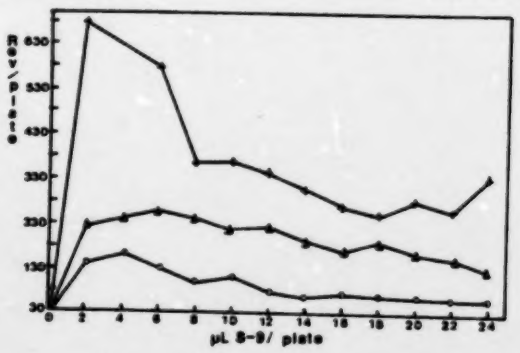


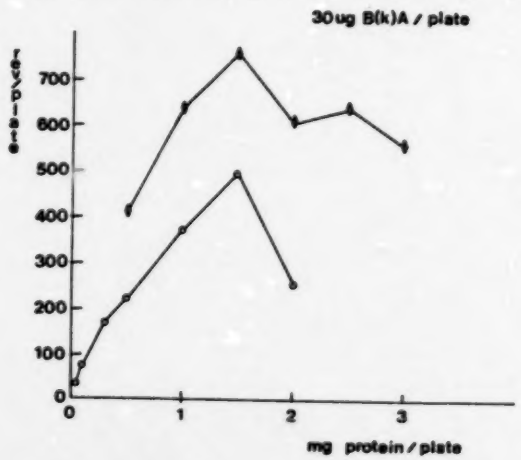
FIGURE 22. S-9 dependence of mutagenicity for: +, benz(e)aceanthrylene; Δ, benz(e)aceanthrylene; o, benz(j)aceanthrylene. Protein concentration is 25.7 mg/ml



the case of benzo(a)pyrene diolepoxide, serves only to detoxify the reactive cyclopenta epoxide initially produced.[4] Hence the optimum protein concentrations for activation of I-III are 0.1-0.3 mg/plate compared to >2 mg/plate for BP. Additional support for one-step activation of I-III via cyclopenta-epoxides can be drawn from the identification of the cyclopenta dihyrodiols as major metabolites and from the observation that the 1,2 oxide of III (synthesized by m-chloroperoxybenzoic acid oxidation) is a direct acting mutagen having 5-fold greater activity than an equimolar amount of III+S9. The S-9 dependence of mutagenicity for I-III is similar to that reported for cyclopenta- (cd)pyrene[1] and evidence strongly implicates epoxidation of the 5-membered ring[2] of cyclo-
penta(cd)pyrene as the activating step.

The optimum protein concentration for mutagenicity of IV (Figure 23) in TA 98 lies between that of BP and the benzaceanthrylene isomers I-III, suggesting that activation may pro-

FIGURE 23. Protein dependence of mutagenicity for benz(k)acephenanthrylene (2 experiments shown)



ceed via intermediates other than (or in addition to) the cyclopenta-oxide. This result is in accord with the hypothesis[12] that large $\Delta E_{deloc}/\beta$ is an important prerequisite for biological activity.

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CYCLOPENTA-FUSED ISOMERS OF BENZ(a)ANTHRACENE: IDENTIFICATION OF MAJOR MICROSOMAL METABOLITES

KEYWORDS

metabolites of benz(j)aceanthrylene
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